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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
10/817,204	04/02/2004	Nagi G. Ayad	10498-00067	3911

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EXAMINER	
LEE, JAE W	

ART UNIT	PAPER NUMBER
1656	

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Please find below and/or attached an Office communication concerning this application or proceeding.

The time period for reply, if any, is set in the attached communication.

Office Action Summary	Application No.	Applicant(s)	
	10/817,204	AYAD ET AL.	
	Examiner	Art Unit	
	JAE W. LEE, PhD	1656	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE *3* MONTH(S) OR THIRTY (30) DAYS, WHICHEVER IS LONGER, FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *17 December 2007*.

2a)☐ This action is **FINAL**. 2b)☒ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *1,3-13 and 26* is/are pending in the application.

4a) Of the above claim(s) _____ is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *1,3-13 and 26* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☒ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☒ Information Disclosure Statement(s) (PTO/SB/08) Paper No(s)/Mail Date *06/05/2007*.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____ .
5) ☐ Notice of Informal Patent Application
6) ☐ Other: _____.

DETAILED ACTION

Application Status

A request for continued examination under 37 CFR 1.114, including the fee set forth in 37 CFR 1.17(e), was filed in this application after final rejection. Since this application is eligible for continued examination under 37 CFR 1.114, and the fee set forth in 37 CFR 1.17(e) has been timely paid, the finality of the previous Office action has been withdrawn pursuant to 37 CFR 1.114. Applicant's submission filed on 12/17/2007 has been entered.

In response to the previous Office actions, a final rejection (mailed on 06/15/2007), Applicants filed a response and amendment received on 12/17/2007. Said amendment, amended Claims 1-3, 5 and 6. Claims 1, 3-13 and 26 are at issue and present for examination.

Applicants' arguments filed on 12/17/2007, have been fully considered, and are deemed to be persuasive to overcome some of the rejections previously applied. Rejections and/or objections not reiterated from previous office actions are hereby withdrawn.

The text of those sections of Title 35 U.S. Code not included in the instant action can be found in a prior Office action.

It is noted by the Examiner that Claims 14-25 and 27-51 were withdrawn from further consideration by the Examiner, 37 CFR 1.142(b) as being drawn to a non-elected invention, in the previous Office actions, a non-Final rejection (mailed on 12/29/2006).

Information Disclosure Statement

Applicants' filing of information disclosure, filed on 06/05/2007, is acknowledged. Those references considered have been initialed, while those missing references or having no date have been lined through.

Claim Rejections - 35 USC § 112

The following is a quotation of the second paragraph of 35 U.S.C. § 112:

> The specification shall conclude with one or more claims particularly pointing out and distinctly claiming the subject matter which the applicant regards as his invention.

The previous rejection of Claims 1, 2, 7-13 and 26 under of 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention, is withdrawn by virtue of Applicants' amendment because the Tome-1 activities are listed in a) through j) in claims 1.

The following is a quotation of the first paragraph of 35 U.S.C. § 112:

> The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

Claims 1, 2-13 and 26 are rejected under 35 U.S.C. § 112, first paragraph, written description, as failing to comply with the written description requirement. The claim(s) contains subject matter which was not described in the specification in such a way as to reasonably convey to one skilled in the relevant art that the inventor(s), at the time the application was filed, had possession of the claimed invention.

The rejection was stated in the previous office action as it applied to previous claims 1-13 and 26. In response to this rejection, Applicants have cancelled claim 2, and amended claims 1, 3 and 5, and traverse the rejection as it applies to the newly amended claims.

Applicants point out that claims 1, 3, and 5 have been amended to explicitly recite the following Tome-1 activities: (1) modulating ubiquitinylation of wee1 protein; (2) modulating degradation of wee1 protein (3) modulating SCF complex components; (4) modulating entry of a cell into the cell cycle; (5) modulating progression of a cell through the cell cycle; (6) modulating release of a cell from the cell cycle; (7) modulating cell growth; (8) modulating cellular proliferation; (9) modulating tumorigenesis; and (10) modulating mitogenesis. Applicants note that one of skill in the art would understand that the unicellular and multi-cellular prokaryotes that do not undergo mitosis would not have a protein that would trigger mitotic entry. In addition, Applicants point out that claims 1, 3, and 5 have been amended to recite that the nucleic acid sequence is from a eukaryotic cell. Based on this amendment, Applicants allege that one of

skill in the art would have recognized that Applicants had possession of the claimed sequences at the time of filing.

Applicants' arguments have been fully considered but are not deemed persuasive for the following reasons. First, claims are drawn to a genus of isolated nucleic acid molecules from a eukaryotic cell, [1] wherein said nucleic acid molecules comprises any nucleic acid sequence with at least about 60% sequence homology to a nucleic acid comprising a nucleotide sequence selected from the group consisting of SEQ ID NO:4, SEQ ID NO:5 and SEQ ID NO:6, or [2] which encodes a polypeptide comprising any amino acid sequence having at least about 60% sequence homology to an amino acid sequence selected from the group consisting of SEQ ID NO: 1, SEQ ID NO:2 and SEQ ID NO:3, wherein the polypeptide has one or more trigger of mitotic entry 1 (Tome-1) activities; wherein said activities are selected from the group consisting of: a) modulating ubiquitinylation of wee1 protein; b) modulating degradation of wee1 protein; c) modulating Skp-Cullin-F-box protein complex (SCF complex) components, wherein said components are Skp-1, Cul-1, Rbx and an F Box substrate; d) modulating entry of a cell into the cell cycle; e) modulating progression of a cell through the cell cycle; f) modulating release of a cell from the cell cycle; g) modulating cell growth; h) modulating cellular proliferation; i) modulating tumorigenesis; and j) modulating mitogenesis. In other words, the recited genus of isolated nucleic acid sequences encompasses any polynucleotide sequences [1] having at least 60% sequence homology to SEQ ID NOs: 4-6, or [2] which encodes any amino acid sequence having at least 60% sequence homology to

SEQ ID NOs: 1-3, as long as the encoded protein has the broadly defined functions or activities as recited in a) through j). Such a broad genus of isolated nucleic acid molecules with widely variant structures, wherein the proteins encoded by said nucleic acid molecules have many different broadly defined functions/activities as recited in a) through j) are not adequately described by the disclosure of the specification because said disclosure is limited to polynucleotides having the nucleotide sequences of SEQ ID NOs: 4-6 which encode the mouse, human and Xenopus Tome-1 proteins as set forth in SEQ ID NOs: 1-3, respectively, wherein said Tome-1 proteins interact with phosphorylated Wee1 for ubiquitination-dependent Wee-1 degradation. The reason is that a complex network of proteins having widely variant biological activities, i.e., widely variant activities of cell-cycle check point proteins at [1] G0, [2] G1, [3] S, [4] intra S, [5] G2 and [6] M just to mention a few, are required for modulating entry of a cell into the cell cycle. As such, widely variant functions/activities described in d)-j) of claim 1, are not described by the specification. Furthermore, widely variant nucleic acid sequences encoding proteins having mere 60% sequence homology to SEQ ID NOs 1-3 with widely variant functions, i.e., especially those activities recited in d) through j) in claim 1, are not adequately described by the specification. It is well-known and accepted in the relevant art that proteins having very similar structure can have different activities. See Witkowski et al., (Biochemistry, 38, 11643-11650, 1999), and Wishart et al., (Journal of Biological Chemistry, Vol. 270, No. 45, pp. 26782–26785, 1995). In light of this notion, one of skill in the art would not have

recognized that Applicants were in possession of any isolated nucleic acid molecule [1] having at least 60% sequence homology to SEQ ID NOs: 4-6, or [2] which encodes any amino acid sequence having at least 60% sequence homology to SEQ ID NOs: 1-3, in addition to having widely variant functions as described in d)-j) of claim 1.

With regard to Claim 4, the recitation of "a nucleotide sequence selected from the group consisting of SEQ ID NO: 4, SEQ ID NO: 5 and SEQ ID NO: 6," can be interpreted any nucleotide sequence selected from the group consisting of SEQ ID NO: 4, SEQ ID NO: 5 and SEQ ID NO: 6, including any fragment thereof. However, such a broad genus of polynucleotide fragments having any function is not described by the specification.

Please refer to the M.P.E.P. section 2163 [R-5] under II, A, 3, (a), (ii) for more details with respect to sufficient number of representative species that should be disclosed to describe a widely variant genus.

Given the lack of additional representatives of a genus of isolated nucleic acid molecules [1] having at least 60% sequence homology to SEQ ID NOs: 4-6, or [2] which encodes any amino acid sequence having at least 60% sequence homology to SEQ ID NOs: 1-3, in addition to having widely variant functions, as encompassed by the claim, Applicants have failed to sufficiently describe the claimed invention, in such full, clear, concise, and exact terms that a skilled artisan would recognize Applicants were in possession of the claimed invention.

Applicant is referred to the revised guidelines concerning compliance with the written description requirement of U.S.C. 112, first paragraph, published in the Official Gazette and also available at www.uspto.gov.

Claims 1, 3-13 and 26 are rejected under 35 U.S.C. 112, first paragraph, scope of enablement, because the specification, while being enabling for isolated nucleic acid molecules comprising the nucleotide sequences of SEQ ID NOs: 4-6 which encode the mouse, human and Xenopus Tome-1 proteins as set forth in SEQ ID NOs: 1-3, respectively, wherein said Tome-1 proteins interact with phosphorylated Wee1 for ubiquitination-dependent Wee-1 degradation, does not reasonably provide enablement for any isolated nucleic acid molecule [1] having at least 60% sequence homology to SEQ ID NOs: 4-6, or [2] which encodes any amino acid sequence having at least 60% sequence homology to SEQ ID NOs: 1-3, in addition to having widely variant functions as described in a)-j) of claim 1. Therefore, the specification does not enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and/or use the invention commensurate in scope with these claims.

The rejection was stated in the previous office action as it applied to previous claims 1-13 and 26. In response to this rejection, Applicants have cancelled claim 2, and amended claims 1, 3 and 5, and traverse the rejection as it applies to the newly amended claims.

Applicants argue that based on Applicants' newly amended claims, determining whether the nucleic acid sequence encodes a polypeptide having

the claimed sequence identity and has one or more of the recited Tome-1 activities would involve only routine screening of eukaryotic sequences, and therefore this experimentation is not undue.

Applicants' arguments have been fully considered but are not deemed persuasive for the following reasons. First, Claims are so broad to encompass any isolated nucleic acid molecule [1] having at least 60% sequence homology to SEQ ID NOs: 4-6, or [2] which encodes any amino acid sequence having at least 60% sequence homology to SEQ ID NOs: 1-3, in addition to having widely variant functions as described in a)-j) of claim 1. The specification, however, does not support the broad scope of the claims which encompass all modifications and fragments of any isolated nucleic acid molecule [1] having at least 60% sequence homology to SEQ ID NOs: 4-6, or [2] which encodes any amino acid sequence having at least 60% sequence homology to SEQ ID NOs: 1-3, as long as it has widely variant functions as described in a)-j) of claim 1. For instance, the specification does not provide support for making and using an isolated nucleic acid molecule having 60% sequence homology to SEQ ID NO: 4, which *increases* tumorigenesis while *decreasing* cellular proliferation. Furthermore, the specification does not enable one of skill in the art how to make and use an isolated nucleic acid molecule having 60% sequence homology to SEQ ID NO: 4 which *increases only* the cellular proliferation without affecting the tumorigenesis, or vise versa, all of which are encompassed by the claimed language, "one or more Tome-1 activities; wherein said activities are selected from the group consisting of: … modulating cell growth [or cellular proliferation,

tumorigenesis, mitogenesis, etc]." Given the widely variant biological activities that encompassed by the activities recited in d) through j) of claim 1 as explained above, in addition to the notion that proteins having very similar structure can have different activities (see Witkowski et al., and Wishart et al.), it would be undue experimentation for one of skill in the art to make and use the claimed invention.

With regard to Claim 4, the recitation of "a nucleotide sequence selected from the group consisting of SEQ ID NO: 4, SEQ ID NO: 5 and SEQ ID NO: 6," can be interpreted any nucleotide sequence selected from the group consisting of SEQ ID NO: 4, SEQ ID NO: 5 and SEQ ID NO: 6, including any fragment thereof. However, the specification lacks support for any polynucleotide fragments of SEQ ID NOs: 4-6 having the desired biological function.

Taken together, the specification does not enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and/or use the invention commensurate in scope with these claims.

The scope of the claims must bear a reasonable correlation with the scope of enablement (In re Fisher, 166 USPQ 19 24 (CCPA 1970)). Without sufficient guidance, determination of any isolated nucleic acid molecule [1] having at least 60% sequence homology to SEQ ID NOs: 4-6, or [2] which encodes any amino acid sequence having at least 60% sequence homology to SEQ ID NOs: 1-3, in addition to having widely variant functions as described in a)-j) of claim 1 having the desired biological characteristics is unpredictable and the experimentation left

to those skilled in the art is unnecessarily, and improperly, extensive and undue. See In re Wands 858 F.2d 731, 8 USPQ2nd 1400 (Fed. Cir, 1988).

Claim Rejections - 35 USC § 102

Claims 1, 3, 5-13 and 26 are rejected under 35 U.S.C. 102(b) as anticipated by Walker et al. (WO/2002/018575).

The rejection was stated in the previous office action as it applied to previous claims 1-3, 5-13 and 26. In response to this rejection, Applicants have cancelled claim 2, and amended claims 1, 3 and 5, and traverse the rejection as it applies to the newly amended claims.

Applicants argue claims 1, 3-13, and 26 all recite an isolated nucleic acid or depend from claims having this element. However, Applicants allege that Walker et al. do not teach that their SEQ ID NO: 3 nucleic acid was isolated because Walker et al. note that "The invention provides an isolated cDNA having a nucleic acid sequence selected from SEQ ID NOs 1, 2, and 4-10 and the complements thereof" (page 2, lines 21-22). Further, Applicants allege that Walker et al. do not teach SEQ ID NO: 3 with the Tome-1 activities listed in claim 1.

Applicants' arguments have been fully considered but are not deemed persuasive for the following reasons. The reference of Walker et al. teaches the "isolation" of SEQ ID NO: 3 with one of the Tome-1 activities listed in claim 1 because Walker et al. have used the cDNA of SEQ ID NO: 3 to perform recombinant protein expression, and production of specific antibodies against the

protein (see pg. 28-29 of Walker et al.). Even if Walker et al. did not physically clone the SEQ ID NO: 3 themselves from the chromosomal DNA, such information regarding purifying cDNA as set forth in SEQ ID NO: 3, expression and characterization of its encoded protein sequence was previously published as evidenced on pg. 19 of the reference of Walker et al., under CDC23 (see especially Zhao et al. and other references cited therein). It is reproduced herein for the Applicants' convenience.

> "CDC23, cell division cycle protein 23, is a component of the anaphase-promoting complex that regulates mitosis by catalyzing the formation of cyclin B-ubiquitin conjugates, targeting cyclin B for degradation. (Prinz (1998) Curr Biol 8:750-760; Zhao et al. (1998) Genomics 53:184-90; and Hershko (1999) Philos Trans R Soc Lond B Biol Sci 354:1571-1576)"

It is further noted by the Examiner that the reference of Zhao et al. teaches the purification/isolation and characterization of the human CDC23 gene, its cDNA and the encoded protein (see under "RESULTS AND DISCUSSION" on pg. 185, and also Figures 1 and 2 on pg. 186 and 187 of Zhao et al.). In addition, Zhao et al. teach that it is an inherent characteristic of CDC23 to have a biological activity, which promotes exit from mitosis via the degradation of cyclin B because it is a part of APC or anaphase-promoting complex (see pg. 184, right column, 2nd paragraph). Therefore, the CDC23 taught by Walker et al. meets all the claimed limitations of claims 1, 3, 5 and 6. For the reasons provided herein and in the previous office action, the rejection under this statute is maintained.

Claims 1, 3, 5-8, 10 and 26 are rejected under 35 U.S.C. 102(b) as anticipated by Zhao et al. (Human *CDC23:* cDNA Cloning, Mapping to 5q31, Genomic Structure, and Evaluation as a Candidate Tumor Suppressor Gene in Myeloid Leukemias, GENOMICS 53, 184–190, 1998) as evidenced by Walker et al. (WO/2002/018575).

The instant claims are drawn to an isolated nucleic acid molecule from a eukaryotic cell which encodes a polypeptide comprising an amino acid sequence having at least about 60% sequence homology to an amino acid sequence selected from the group consisting of SEQ ID NO: 1, SEQ ID NO: 2 and SEQ ID NO: 3, wherein the polypeptide has one or more trigger of mitotic entry 1 (Tome-1) activities; wherein said activities are selected from the group consisting of: a) modulating ubiquitinylation of wee1 protein; b) modulating degradation of wee1 protein; c) modulating Skp-Cullin-F-box protein complex (SCF complex) components, wherein said components are Skp-1, Cul-1, Rbx and an F Box substrate; d) modulating entry of a cell into the cell cycle; e) modulating progression of a cell through the cell cycle; f) modulating release of a cell from the cell cycle; g) modulating cell growth; h) modulating cellular proliferation; i) modulating tumorigenesis; and j) modulating mitogenesis.

The reference of Zhao et al. teaches the purification/isolation and characterization of the human CDC23 gene, and its cDNA (see under “RESULTS AND DISCUSSION” on pg. 185, and also Figures 1 and 2 on pg. 186 and 187 of Zhao et al.). It is noted by the Examiner that the isolated cDNA of Zhao et al. as shown in Figure 1, which has 97% sequence homology to the Applicant's SEQ ID

NO: 5, encodes an amino acid sequence having at least 60% sequence homology to Applicant's SEQ ID NO: 2 (see the previous sequence alignment provided for the reference of Walker et al. because the nucleic acid sequence of Walker et al. is identical with that of Zhao et al.), as evidenced on pg. 8 and 19 of the reference of Walker et al., under SEQ ID NO: 3, CDC23: "CDC23, cell division cycle protein 23, is a component of the anaphase-promoting complex that regulates mitosis by catalyzing the formation of cyclin B-ubiquitin conjugates, targeting cyclin B for degradation. (Prinz (1998) Curr Biol 8:750-760; Zhao et al. (1998) Genomics 53:184-90; and Hershko (1999) Philos Trans R Soc Lond B Biol Sci 354:1571-1576)." In addition, Zhao et al. teach that it is an inherent characteristic of CDC23 to have a biological activity, which promotes exit from mitosis via the degradation of cyclin B because it is a part of APC or anaphase-promoting complex (see pg. 184, right column, 2nd paragraph), thereby anticipating Claims 1, 3, 5 and 6. Teachings of Zhao et al. also anticipate the limitations of Claims 7, 8 and 26 because it is an inherent property of the nucleotide sequence, which is 97% homologous to the Applicant's SEQ ID NO: 5, to hybridize to and be complementary to the Applicant's SEQ ID NO: 5. Further, Claim 10 is anticipated because the cDNA of Zhao et al. was inserted into a PAC cloning vector (see pg. 189 under "Organization of the Human CDC23 gene"). Therefore, Claims 1, 3, 5-8, 10 and 26 are anticipated by the reference of Zhao et al.

Conclusion

Claims 1, 3-13 and 26 are not allowed for the reasons identified in the numbered sections of this Office action. Applicants must respond to the objections/rejections in each section in this Office action to be fully responsive in prosecution.

This office action is non-final.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Jae W. Lee whose telephone number is 571-272-9949. The examiner can normally be reached on M-F between 10:30-7.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Kathleen Kerr can be reached on 571-272-0931. The fax phone number for the organization where this application or proceeding is assigned is 571-273-8300.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see http://pair-direct.uspto.gov. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free). If you would like assistance from a USPTO Customer Service Representative or access to the automated information system, call 800-786-9199 (IN USA OR CANADA) or 571-272-1000.

/JAE W LEE, PhD/
Examiner, Art Unit 1656

/Richard G Hutson, Ph.D./
Primary Examiner, Art Unit 1652